reverse remodeling drug because the final dose of carvedilol was 25% higher in this treatment arm. This would be expected from previous large-scale beta-blocker trials. Any additional agent on top of what is already working may yield a smaller incremental effect as the investigators also demonstrated in the perindopril-initiated arm.

What this "humble" study confirms are that beta-blockers are important in patients with NYHA functional class II or above, that diligence and patience must be used to up-titrate to the highest dose tolerated, and that we should not withhold use of beta-blockade even if a patient feels better without it. The impact of the study is not which agent to initiate first, but that both must be used without delay.

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Beta-Blocker Treatment Before Angiotensin-Converting Enzyme Inhibitor Therapy in Newly Diagnosed Heart Failure

We read with great interest the study by Sliwa et al. (1) recently published in the *Journal*. In their report they observed that, compared to the commonly recommended order of starting therapy for newly diagnosed heart failure with an angiotensin-converting enzyme inhibitor (ACEI) followed by a beta-blocker, the opposite order of starting with the beta-blocker carvedilol followed by the ACEI perindopril had a superior effect on New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), plasma N-terminal pro-brain natriuretic peptide concentration, and LV volumes. We believe that this is a very important study and the investigators are to be congratulated for their achievement. In his accompanying editorial (2), Dr. Leier points out that a large multicenter morbidity/mortality trial would have to be performed to verify the results obtained by Sliwa et al.

In response to this we would like to inform readers of *JACC* that, based on a hypothesis similar to the one by Sliwa et al., we started planning such a morbidity/mortality trial more than four years ago. The rationale and design of this trial, the Cardiac Insufficiency Bisoprolol Study (CIBIS)-III, has been published (3), and the study is now concluded. In 18 European countries, as well as in Tunisia and Australia, 1,013 patients with NYHA functional class II to III heart failure have been included.

The CIBIS-III trial is designed to provide evidence for the best order of initiating therapy. The end point rate is as expected, ensuring an adequate statistical power to show noninferiority or superiority for bisoprolol-first, should that be the case. If superiority for either treatment regimen is shown we will know if we generally should start heart failure therapy with an ACEI or a beta-blocker. If the trial shows noninferiority for bisoprolol-first versus enalapril-first, there is evidence supporting a free choice with regard to the first therapy, based on individual judgment in each patient. A result showing that bisoprolol-first is superior to enalapril-first will challenge the paradigm of testing compounds for the treatment of heart failure against a background of ACEI therapy.

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Treatment Order in Managing Systolic Ventricular Dysfunction

Dr. Leier (1) has made a useful and provocative commentary on the work of Sliwa et al. (2). Clearly Dr. Leier is impressed by the principle of testing order effects in the management of systolic left ventricular (LV) dysfunction. This is a very wise and long overdue assessment although not performed in a double-blinded randomized crossover design that would be expected to characterize an order effect. It would be equally wise to retain balance in estimating the impact or generalizability of this work.

First, it is often forgotten that all modern studies in systolic failure involve structured addition of therapy to established treatments. Although we often focus on the added therapy we tend to ignore the baseline, which is constantly changing and makes proving efficacy of a new addition consequently more challenging. For example, all patients in the angiotensin-converting enzyme (ACE) inhibitor, ino-dilator, or vasodilator and digoxin systolic failure trials of the 1980s and 1990s were subjected to loop diuretic therapy, which has a powerful impact in stimulating the circulating and tissue-based (renin-angiotensin-aldosterone system). The well-characterized and accepted adverse effects of the changes caused by these treatments are balanced in the individual patient by the beneficial effect on fluid volume and loading. Although